heterocyclic ring including two nitrogen atoms." Furthermore, the Examiner agreed that such language would not pose an enablement problem in view of the Schlama reference previously submitted by the Applicants. Applicants agree to the proposed amendments, which are entered herewith, among others.

In reply to the Examiner's Action mailed December 19, 2003, and the telephonic interview of February 18, 2004, Applicants submit the following Amendments and Remarks.

AMENDMENT

Kindly amend the application as follows.

In the Claims:

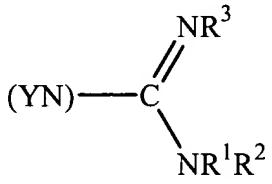
Please amend claims 1, 7, 8, 10, 19, 20, 21, 22, and 34 as outlined in the following claims listing.

Claims Listing:

1. (Currently Amended) A compound having the formula:

(YN)-(spacer)-(amidine or guanidine group)

or



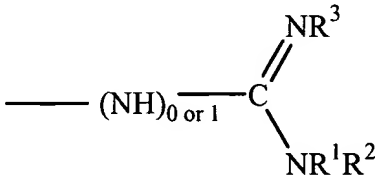
wherein

(YN) is an organic residue obtained by the removal of a predetermined organic group, ~~Q~~ R, from an opioid of the formula ~~YN-Q~~ YN-R, said opioid selected from the group consisting of morphine, codeine, heroin, ethylmorphine, O-

carboxymethylmorphine, O-acetylmorphine, hydrocodone, hydromorphone, oxymorphone, oxycodone, dihydrocodeine, thebaine, metopon, ethorphine, acetorphine, diprenorphine (M5050), buprenorphine, phenomorphan, levorphanol, pentazocine, eptazocine, metazocine, ethoheptazine, ketobemidone, dihydroetorphine and dihydroacetorphine;

(spacer) is a group linking YN to an amidine or guanidine group, wherein YN and said amidine or guanidine group are separated by 1 to 6 carbon atoms; and

(amidine or guanidine group) is a group of the formula



in which

R^1 is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;

R^2 is H or an alkyl group having 1 to 6 carbon atoms;

R^3 is H, alkyl, hydroxy, amino, cyano or acyl, wherein alkyl and acyl have 1 to 6 carbon atoms; or

R^1 and R^3 together ~~form an alkylene or alkenylene of from 2 to 4 carbon atoms to~~ complete a heterocyclic ring including two nitrogen atoms,

or a pharmaceutically acceptable salt thereof,

wherein said compound acts as an analgesic that has reduced sedative or addictive effect in comparison to any opioid of formula ~~YN-Q~~ YN-R wherein ~~comprising an organic residue~~ YN of YN-R is identical to ~~the organic residue~~ YN of said

compound and R of YN-R is H, -$CH_2CH=CMe_2$, phenethyl, cyclopropyl, or an alkyl of 1 to 6 carbon atoms.

2. (Previously Presented) A compound according to Claim 1, in which the spacer is a straight or branched alkyl, alkenyl or alkynyl chain of 1 to 6 carbon atoms.

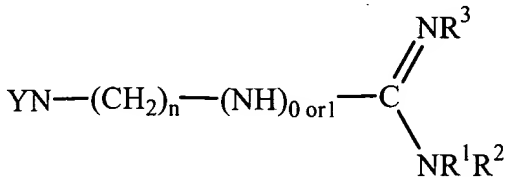
3. (Previously Presented) A compound according to Claim 1, in which the spacer is a cyclic alkyl, alkenyl or alkynyl group.

4. Canceled.

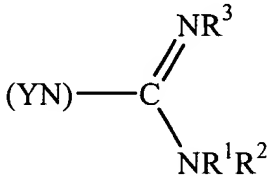
5. (Previously Presented) A compound according to Claim 1, in which the spacer group is of 2 to 3 carbon atoms.

6. Canceled.

7. (Currently Amended) A compound according to Claim 1, of formula:



or



wherein

(YN) is an organic residue obtained by the removal of a predetermined organic group, ~~Q~~ R, from an opioid of the formula ~~YN-Q~~ YN-R, said opioid selected from the group consisting of morphine, codeine, heroin, ethylmorphine, O-carboxymethylmorphine, O-acetylmorphine, hydrocodone, hydromorphone, oxymorphone, oxycodone, dihydrocodeine, thebaine, metopon, ethorphine, acetorphine, diprenorphine (M5050), buprenorphine, phenomorphan, levorphanol,

pentazocine, eptazocine, metazocine, ethoheptazine, ketobemidone, dihydroetorphine and dihydroacetorphine;

in which

R^1 is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;

R^2 is H or an alkyl group having 1 to 6 carbon atoms;

R^3 is H, alkyl, hydroxy, amino, cyano or acyl, wherein alkyl and acyl have 1 to 6 carbon atoms; or

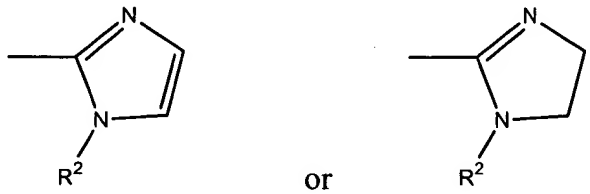
R^1 and R^3 together ~~form an alkylene or alkenylene of from 2 to 4 carbon atoms to~~ complete a heterocyclic ring including two nitrogen atoms; and

n is an integer of 1 to 6;

or a pharmaceutically acceptable salt thereof.

8. (Currently Amended) A compound according to Claim 7, in which R^1 and R^3 together ~~form an alkylene or alkenylene of from 2 to 4 carbon atoms to~~ complete a heterocyclic ring including two nitrogen atoms.

9. (Original) A compound according to Claim 8, in which the heterocyclic moiety is a 2-imidazolyl or 2-imidazolinyl group of formula:



10. (Currently Amended) A compound according to Claim 8 or Claim 9, in which ~~R~~ R^2 is CH_3.

11. (Previously Presented) A compound according to Claim 8, in which n is 2 or 3.

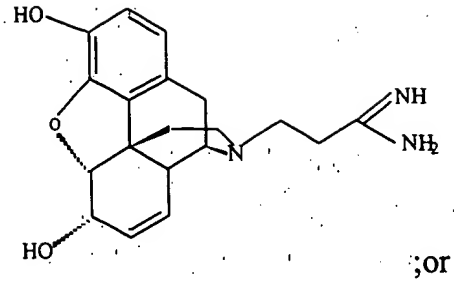
12. (Previously Presented) A compound according to Claim 7, in which R^1 and R^2 are both H.

13. Canceled.

14. (Previously Presented) A compound according to Claim 7 , in which the opioid is morphine, codeine or buprenorphine.

15. Canceled.

16. (Previously Presented) A compound according to Claim 1, said compound selected from the group consisting of



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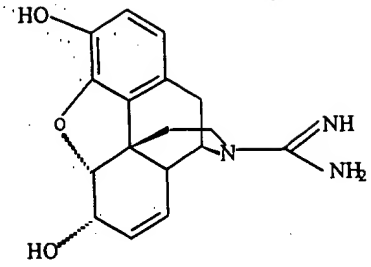

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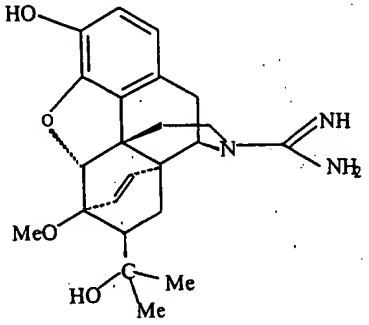

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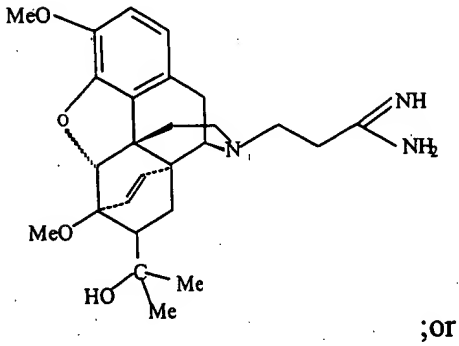

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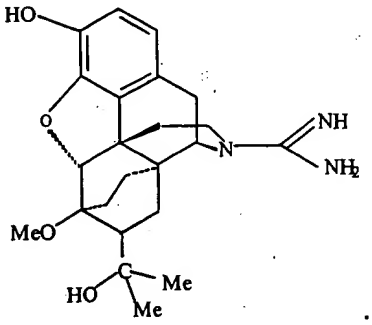

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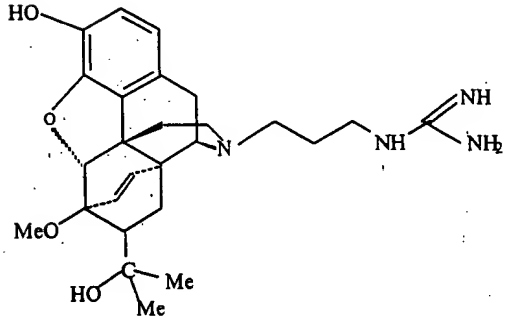

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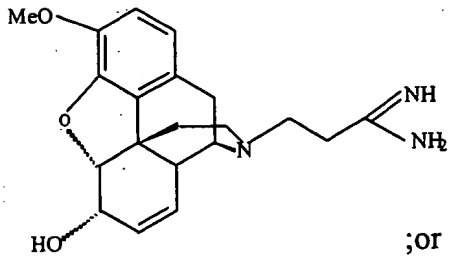

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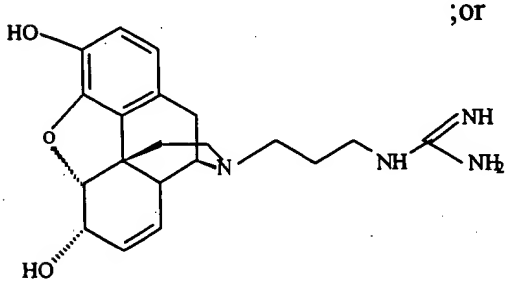

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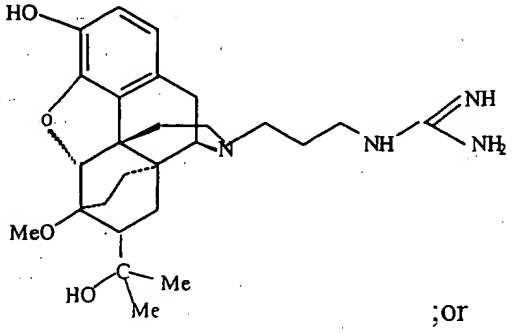

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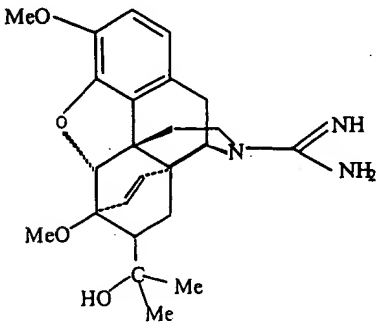
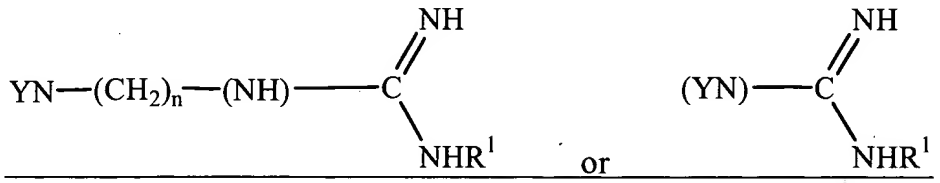


17. Canceled.

18. Canceled.

19. (Currently Amended) A method for the preparation of a compound of ~~claim 7~~ formula:



wherein

(YN) is an organic residue obtained by the removal of a predetermined organic group, R, from an opioid of the formula YN-R, said opioid selected from the group consisting of morphine, codeine, heroin, ethylmorphine, O-carboxymethylmorphine, O-acetylmorphine, hydrocodone, hydromorphone, oxymorphone, oxycodone, dihydrocodeine, thebaine, metopon, ethorphine, acetorphine, diprenorphine (M5050), buprenorphine, phenomorphan, levorphanol, pentazocine, eptazocine, metazocine, ethoheptazine, ketobemidone, dihydroetorphine and dihydroacetorphine;

in which

R^1 is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms; and

n is an integer of 1 to 6;

comprising the step of reacting a compound having the formula

$YN\text{-}(CH_2)_n\text{-}NH_2$

or

YN-H

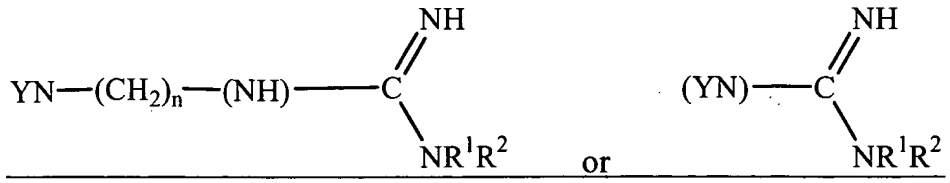
with a cyanamide of formula R^1NHCN, ;

~~wherein~~

~~R^1 is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms; and~~

~~n is an integer of 1 to 6.~~

20. (Currently Amended) A method for the preparation of a compound of ~~claim 7~~ formula:



wherein

(YN) is an organic residue obtained by the removal of a predetermined organic group, R, from an opioid of the formula YN-R, said opioid selected from the group consisting of morphine, codeine, heroin, ethylmorphine, O-carboxymethylmorphine, O-acetylmorphine, hydrocodone, hydromorphone, oxymorphone, oxycodone, dihydrocodeine, thebaine, metopon, ethorphine, acetorphine, diprenorphine (M5050), buprenorphine, phenomorphan, levorphanol, pentazocine, eptazocine, metazocine, ethoheptazine, ketobemidone, dihydroetorphine and dihydroacetorphine;

in which

R^1 is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;

R^2 is H or an alkyl group having 1 to 6 carbon atoms; and

n is an integer of 1 to 6;

comprising the steps of reacting a compound of formula

~~$YN-(CH_2)_n-(NH)_{0 \text{ or } 1}-CN$~~

$YN-(CH_2)_n-(NH)-CN$

or

YN-CN

with H_2S to obtain an N-thiocarboxamide , and then either

(i) reacting the N-thiocarboxamide with an amine R^1R^2NH, or

(ii) Methylating the N-thiocarboxamide to yield an isothiourea compound, which is in turn reacted with an amine R^1R^2NH, ;

~~wherein~~

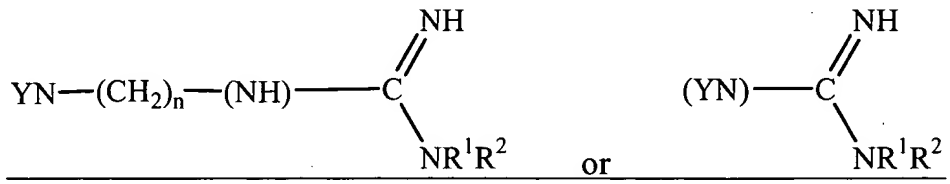
~~R^1 is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;~~

~~R^2 is H or an alkyl group having 1 to 6 carbon atoms;~~

~~R^3 is H; and~~

~~n is an integer of 1 to 6.~~

21. (Currently Amended) A method for the preparation of a compound of ~~claim 7~~ formula:



wherein

(YN) is an organic residue obtained by the removal of a predetermined organic group, R, from an opioid of the formula YN-R, said opioid selected from the group consisting of morphine, codeine, heroin, ethylmorphine, O-carboxymethylmorphine, O-acetylmorphine, hydrocodone, hydromorphone, oxymorphone, oxycodone, dihydrocodeine, thebaine, metopon, ethorphine, acetorphine, diprenorphine (M5050), buprenorphine, phenomorphan, levorphanol, pentazocine, eptazocine, metazocine, ethoheptazine, ketobemidone, dihydroetorphine and dihydroacetorphine;

in which

R^1 is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;

R^2 is H or an alkyl group having 1 to 6 carbon atoms; and

n is an integer of 1 to 6;

comprising the step of reacting a compound of formula

$$YN\text{-}(CH_2)_n\text{-}(NH)\text{-}CN$$

or

$$YN\text{-}CN$$

with methanol under acidic conditions to yield an isourea, which in turn is reacted with an amine of the formula R^1R^2NH;

~~wherein~~

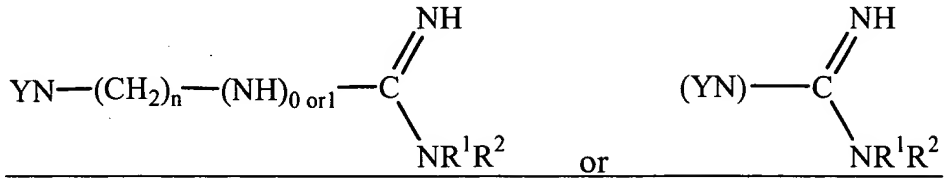
~~R^1 is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;~~

~~R^2 is H or an alkyl group having 1 to 6 carbon atoms;~~

~~R^3 is H; and~~

~~n is an integer of 1 to 6.~~

22. (Currently Amended) A method for the preparation of a compound of ~~claim 7~~ formula:



wherein

(YN) is an organic residue obtained by the removal of a predetermined organic group, R, from an opioid of the formula YN-R, said opioid selected from the group consisting of morphine, codeine, heroin, ethylmorphine, O-carboxymethylmorphine, O-acetylmorphine, hydrocodone, hydromorphone, oxymorphone, oxycodone, dihydrocodeine, thebaine, metopon, ethorphine, acetorphine, diprenorphine (M5050), buprenorphine, phenomorphan, levorphanol, pentazocine, eptazocine, metazocine, ethoheptazine, ketobemidone, dihydroetorphine and dihydroacetorphine;

in which

R^1 is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;

R^2 is H or an alkyl group having 1 to 6 carbon atoms; and

n is an integer of 1 to 6;

comprising the step of reacting a compound of formula

~~YN-(CH$_2$)$_n$-(NH)-CN~~

YN-$(CH_2)_n$-$(NH)_{0 \text{ or } 1}$-CN

or

with a metallated residue containing - NR^1R^2 ;

~~wherein~~

~~R^1 is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;~~

~~R^2 is H or an alkyl group having 1 to 6 carbon atoms;~~

~~R^3 is H; and~~

~~n is an integer of 1 to 6.~~

23. (Previously Presented) A composition comprising a compound according to Claim 1, together with a pharmaceutically acceptable carrier.

24. (Previously Presented) A method of inducing analgesia, comprising the step of administering an effective amount of a compound according to Claim 1 to a mammal in need of such treatment.

25. (Original) A method according to claim 24, in which the mammal is a human.

26. Canceled.

27. Canceled.

28. (Previously Presented) A method of inducing analgesia, comprising the step of administering an effective amount of a compound according to claim 7 to a mammal in need of such treatment.

29. (Previously Presented) A method according to claim 28, in which the mammal is a human.

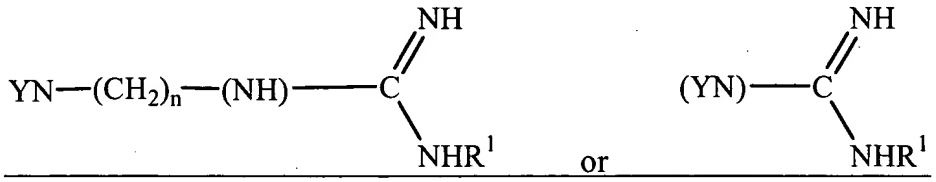
30. Canceled.

31. (Previously Presented) A composition comprising a compound according to Claim 7, together with a pharmaceutically acceptable carrier.

32. Canceled.

33. (Previously Presented) A method of inducing analgesia in a mammal, said method comprising administration of a pharmaceutical composition of claim 23 in amounts effective to induce said analgesia to a mammal in need thereof.

34. (Currently Amended) A method for the preparation of a compound of ~~claim 7~~ formula:



wherein

(YN) is an organic residue obtained by the removal of a predetermined organic group, R, from an opioid of the formula YN-R, said opioid selected from the group consisting of morphine, codeine, heroin, ethylmorphine, O-carboxymethylmorphine, O-acetylmorphine, hydrocodone, hydromorphone, oxymorphone, oxycodone, dihydrocodeine, thebaine, metopon, ethorphine, acetorphine, diprenorphine (M5050), buprenorphine, phenomorphan, levorphanol, pentazocine, eptazocine, metazocine, ethoheptazine, ketobemidone, dihydroetorphine and dihydroacetorphine;

in which

R^1 is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms; and

n is an integer of 1 to 6;

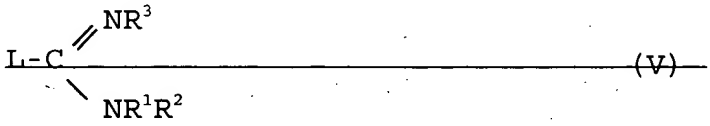
comprising the step of reacting a compound having the formula

$$YN\text{-}(CH_2)_n\text{-}NH_2$$

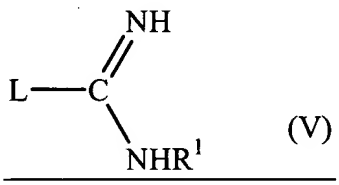
or

YN-H

with a compound of formula (V)



(V)



(V)

wherein R^1 is as defined above,

~~R^1 is H, alkyl or aryloxyalkyl, wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and alkyl, alkoxy and the alkyl moiety of aryloxy alkyl have 1 to 6 carbon atoms;~~

~~R^2 is H or an alkyl group having 1 to 6 carbon atoms;~~

~~R^3 is H, alkyl, hydroxy, amino, cyano or acyl, wherein alkyl and acyl have 1 to 6 carbon atoms;~~

~~n is an integer of 1 to 6,~~

~~and wherein~~

~~R^1 and R^3 may together be an alkylene or alkenylene of from 2 to 4 carbon atoms to complete a ring between the two nitrogen atoms~~, and

L is a leaving group.